APPENDIX 3

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF OHIO
WESTERN DIVISION

----------x

J.B.D.L., d/b/a/ BECKETT APOTHECARY, et al,

Plaintiffs,

-against-

Index No. 1-01-704

WYETH-AYERST LABORATORIES, INC., et al,

Defendants.

----------x

DEPOSITION OF PHILIP SARREL

New York, New York

Thursday, June 3, 2004

Reported by:
Judith A. Frost
Job No.: 161145

A This rebuttal report is a response to a statement by a Professor Hammond, and in looking through this it was clear that was relevant to this case as I was not responding to a statement of Professor Hammond, I was writing my own statement of opinion, and these are aspects of it which obviously did not belong in the new report.

Q So, in other words, you reviewed your old report and you struck out certain things that you didn't want to put in the new report, and things that weren't struck out were things that you intended to put into the new report; is that correct?

A Yes, basically.

Q The next item is a letter dated April 20, 2004, a fax cover sheet from Garwin & Brancef to yourself, and that's something that was sent to you by the plaintiffs in this case; is that right?

A Yes.

Q Attached is a copy of your expert report; is that correct?

MS. BARTELLI: Objection.

A What is the date on that?

Q April 20, 2004.

A I brought that with me so I would know the address to come to this morning. It's on their letterhead.

Q It appears to me that the documents following this cover sheet accompanied the fax since they appear to be faxes at the same time starting with page two?

A Yes, they do.

Q So the following page which is a copy of the report or that draft of that report were sent to you by fax?

A Yes.

Q It appears that this copy of your report is signed, so even though your report is dated April 23, 2004, had you signed it by April 20, 2004?

A Let me take a look at that. It's likely I took three days to review it and then signed it.

Q I see.

So when you signed the report you signed a fax of it that was sent to you by the plaintiff's lawyers?

A That's how this appears, yes. This one.

Q Did you fax the signature page back?

A I don't recall.

Q The next item is an article from the Women's Health Initiative committee, and this is the report on WHI; is that correct?

A That's correct.

Q Is this the first or the second report?

A I believe it's the second. This is April 14, 2004 so this would have been the second report.

Q Is that something you reviewed and relied on in connection with your report?

A Yes.

Q The next is an article by an A. McLennan and S. Lester and V. Moore entitled "Oral Estrogen Replacement Therapy Versus Placebo For Hot Flushes" also prepared for review?

Is this a document that you reviewed in preparation of your report?

A Yes, it is.

Q There appears to be a couple of items torn out of the magazine and publication.

Is there a magazine that you are aware of called "Female Patient"?

A Yes.

Q Is this a magazine to which you can subscribe?

A It's a medical journal that is published by the North American Menopause Society and it's one of the journals of the society.

Q You subscribe for copies?

A All members of the organization receive that.

Q This is an article by Wolf Utian, which is one of the individuals you mentioned earlier, right?

A Yes, he's the executive director.

Q Is this a document that you reviewed in connection with the preparation of your report in this case?

A Yes, it is.

Q Then next is an article which appears to be a fax copy of an article that was faxed to you on about April 18 of 2004; is that correct?

A Yes.

Q It's from the Journal of New Developments in Clinical Medicine?

A That's correct.

Q Before you received this fax had you

seen a copy of this article?
A I had not seen a copy of the article.
Q Do you from time to time review the periodical Journal of New Developments in Clinical Medicine?
A I'm not a reviewer of that journal, no.
Q Do you read copies of it when it comes out?
A When they are relevant to my field of interest, yes.
Q Are you aware of whether or not articles that appear in this journal are peer reviewed?
A They are peer reviewed.
Q What is the system for peer review at the Journal of New Developments in Clinical Medicine?
A I have no idea.
Q How do you know that that it is peer reviewed?
A It's listed as a peer reviewed journal.
Q Where would that listing be? Who maintains a list of peer reviewed journals?

A I don't know the answer to that. I'm under the understanding that was a peer reviewed journal, that that is a peer reviewed journal.
Q What is the basis for your understanding?
A I believe it's in their description.
Q In this fax here?
If you would like to take a look at it and tell me where it says it's a peer reviewed journal.
A I would guess it does not say that in this. It doesn't say that in there.
Q Where would one go to determine whether a particular journal is peer reviewed?
MS. BARTELLI: Objection.
Q Would you look in the journal itself?
A No.
Q How would you determine whether or not a journal is peer reviewed?
MS. BARTELLI: Objection.
A I know that the journals I work for are peer reviewed and are given ratings as to their review status and that is made clear to editors of the journals.
Otherwise, I'm not sure how the

general public would have access to that information. I imagine that there is a mechanism for that but I don't know the mechanism. I know as an editor.
Q What are the ratings that you spoke of?
A Journals have different ratings depending on their previous publications and the assessment of the science of the papers with their publications.
To my knowledge the editors of journals are sent a report. For example, the Journal of North American Menopause Society as an editor at the once a year editorial meeting we are presented with a letter from an accredited body, and my image is there is a national accrediting body that rates the journals.
Q You are not aware of what it is called?
A No.
Q Is it associated with NAMS or would this be a broader body covering a variety?
A This is a broader body covering all the scientific journals.
Q Are you aware of how the Journal of

New Developments in Clinical Medicine rates?
A No.
Q You did rely on that?
Did you rely on this article from the Journal of New Developments in Clinical Medicine, an article by Dr. Hess and a Michael Jay Schwartz in connection with your report?
A I cite that in my report.
Q You are generally familiar and up-to-date with developments in the literature and in the field of estrogen therapy?
MS. BARTELLI: Objection.
A Yes.
Q You weren't aware that this article existed until you received it by fax on April 18, 2004?
MS. BARTELLI: Objection.
A I was aware that the article existed because Dr. Hess told me he had written an article.
Q Did you have conversations with Dr. Hess in the preparation your report in this case?
A No.
Q Under what circumstances did Dr. Hess tell you that he had written the article?

Page 94

of such alternative therapies?
A I think it's important to keep our focus on post-menopausal women and the symptoms they develop.
From that perspective, if you stay focused on that cohort, then I believe that the findings with alternative therapies and herbal prescriptions have shown that they are inadequate to meet a woman's needs.
Q That's your opinion that they are inadequate to meet their needs?
A I'm basing that statement on recent, by recent I mean 2004 summary discussions of what has been shown in the literature for use of alternative therapies in women's health.
Let's take something simple, the control of hot flashes. Many of claims that are made for alternatives therapies and herbals do not stand up to proper research investigation.
Q Incidentally, do you have any formal training in the area of psychiatry?
A Yes.
Q What is the nature of your formal training?
A I do not have my boards in psychiatry,

Page 95

I have my board certifications in obstetrics and gynecology.
Between 1966 and 1967 I spent a year at Yale that was divided between a residency in obstetrics and gynecology and working under the supervision of a psychoanalyst at the Yale Psychiatric Institute.
Q Do you have any --
A I then spent 35 years in the department of psychiatry attending and receiving CME credit. Continuing medical education credit for weekly rounds in psychiatry which I essentially attended every week for 35 years and presented case material.
In the early years of my work from 1969 until 1974 my therapy work was supervised by members of the staff of the department of psychiatry, and then in the 1974/1975 I devoted a year to working in the department of psychiatry at Oxford University in Oxford, England where I was trained in behavioral therapy.
Q Do you have any degrees in the field of psychiatry?
A No, I was designated assistant professor of psychiatry at Yale and then associate

Page 96

professor having met the criteria established in the department of psychiatry.
Q Which did not include a degree in psychiatry, right?
A However, my mentors felt I would be better off without that degree.
Q If you can look at paragraph nine, does this set forth the nature of what you understood your assignment to be in this case?
A Yes.
Q Who gave you that assignment?
A The attorneys for the present firm. This was derived from discussions.
Q The attorneys who are present at this deposition?
A Well, in particular, Ms. Bartelli.
Q The fourth item says advantages of Cenestin, a more technically advanced product, and the advantage is what?
A Advantages with respect to treatment.
Well, if we go to the sense of the provision of optimal hormone treatment, advantages of Cenestin with respect to the provision of optimal menopausal hormone related treatment.
Q Have you expressed any views in here

Page 97

as to the advantages of Cenestin vis-a-vis advantages of a transdermal patch?
A I think I have expressed a generic opinion as to the advantage of delivering a therapeutic stable level of estrogen in the treatment of post menopausal hormone deficiency, and I have not excluded from that the use of transdermal estrogen.
Q The fifth item is the significance of formulary obstacles to optimal treatment?
A Yes.
Q Do you consider yourself to be an expert in the area of formulary obstacles to optimal treatment?
A I consider myself someone who has listened to many physicians across the country, as well as within my own community, and have learned from them that there are formidable obstacles to getting for their patients the medications they want their patients to have.
Q Do you have any personal experience with formulary obstacles to treatment?
MS. BARTELLI: Objection.
A Fortunately in the Yale health plan, which is established is my workplace, we are not

restricted and we can prescribe, all of the physicians can prescribe what each and every one of us believes is best treatment, and then our health plan will cover that medication for the subscribers to the health plan.

From a personal point of view then I have not been subjected to the kinds of barriers or controls that other doctors have had to confront.

Q Have you ever taken any courses or done any study on the area of managed care or formularies?

A No.

Q If you turn to paragraph 13 of your declaration, I awe struck in this paragraph where you said that estrogens known to stimulate more than 400 actions, and it affects throughout the body.

Would you agree that the actions of estrogen in the female body are quite complex?

A Yes.

Q Would you agree that those mechanisms of actions are not yet fully understood?

MS. BARTELLI: Objection.

A I think there is a greater understanding, a greater understanding.

Q Are fully understood?

A Of the mechanisms.

MS. BARTELLI: Objection. Asked and answered.

Dr. Sarrel, give him a chance to finish the question and then answer.

MR. EGGERT: So is it asked and answered or is it finished?

MS. BARTELLI: Pardon me?

Q Has it been fully explored, is there a full understanding of the mechanism of estrogens in the female body?

MS. BARTELLI: Same objection.

A My response is that there is a greater understanding of the mechanisms of action of steroid hormones including estrogens.

Q Anything else?

A The question specifically asks about mechanisms of action. I think that is very well understood.

Is it fully understood? I don't know that is fully understood.

Q Not alluding to the mechanisms of action, but the impact that estrogens have on the female body, is that fully understood?

A That is a different question.

Mechanism of action is a basic bench science question, and actions in a woman's body, that is ongoing and that is a work in progress.

We have many understandings of actions in a woman's body that are beneficial and detrimental and I am sure we will gain many more.

Q In paragraph 14 you list three common medical conditions that relate to ovarian hormone deficiency over onto page five. The first of those being osteoporosis.

Is that a significant issue with ovarian hormone deficiency, the development of osteoporosis?

A It's one of the recognized complications of ovarian hormone deficiency, the loss of bone structure.

Q One of the most common medical conditions associated with ovarian hormone deficiency?

MS. BARTELLI: Objection.

A It's not the only factor. There are a number of contributing factors. It's among the contributing factors to the development of the common condition of osteoporosis.

Q There are also other contributing

factors to heart disease and stroke, for example?

A Correct.

Q In paragraph 15 at the end of that paragraph you state that hormone withdrawal has recently been recognized to be associated with heart attacks.

What is the basis for that statement? Is there any literature on that?

MS. BARTELLI: Objection. Compound.

A There is an existing literature describing the association between acute estrogen deficiency and the occurrence of a heart attack in women.

Q Could you name some of that literature for me?

A Baer is an important paper. The Japanese have documented that.

In my own review, and I think probably the best reference would be to reference number 66, which as I mentioned earlier is now published.

I summarize within that the recent publications of the association of myocardial infarction and acute depletion of estrogen.

Q You summarize the literature?

A The references are there.

Q So as you sit here you can't provide any support for that statement?
MS. BARTELLI: Objection. Mischaracterizes the testimony and asked and answered.
A I can't provide a reference for that right off the bat.
Q In the course of preparing your report did you check that out to determine whether, in fact, that was the case or did you just go with your impression?
MS. BARTELLI: Objection.
A In preparation of the report I did not check that out. I believed that was a fact.
Q The next sentence you say "Unsurprisingly, physicians prefer to work with drugs whose contents are fully known in which no components such as the chemicals and other substances found in Premarin have been eliminated."
Is there any basis for your statement physicians prefer? Is that based on your trips around the country?
A I think we have referred to that in our previous discussions.
MS. BARTELLI: Please wait until he

has finished with his question.
MR. EGGERT: Otherwise, we don't know whether she is objecting to a question or your answer.
Q Doctors still prescribe a lot of Premarin, right?
MS. BARTELLI: Objection. Vague.
A I imagine they do.
Q There is a lot more Premarin prescribed than Cenestin, isn't there?
MS. BARTELLI: Objection.
A I believe that is correct. I would be surprised if it wasn't correct.
Q That's not withstanding the fact that Premarin contained these other substances whose contents are not fully known?
MS. BARTELLI: Objection.
Q Why doctors prescribe Premarin I think you indicated was a very important subject to be studied and has not been reported upon.
Do you have any expertise as to why doctors prescribe Premarin?
A I have opinions.
Q Do you have any expertise in that area?

MS. BARTELLI: Asked and answered.
A Yes, I think we have discussed this already.
Q Do you have an expertise in that area?
A As to why doctors prescribe Premarin?
Q Yes.
A No, I suppose my expertise is why doctors are disenchanted with Premarin and are looking for something else, and that is based on the feedback I have received over the last two years plus years before that too in the way in which I indicated to you already by listening.
Q In your trips around the country have you had physicians come up to you and say I wish I didn't have to prescribe Premarin but I feel I have to prescribe it even though I would rather prescribe Cenestin?
MS. BARTELLI: Objection. Confusing and mischaracterizes his testimony.
A I have had doctors come to me and say I'm glad to be learning about alternatives that will work for my patients. That I can tell you has happened over and over again.
Q Implicit in that suggestion, they do prescribe those alternatives themselves to their

patient, right?
MS. BARTELLI: Objection.
A Whatever I have described has been the results of treatments and studies done with the FDA or at different meetings or my own basic research and received from the list of lectures titles I talk about. You can see.
Q Has any physician ever told you that he or she was unable to prescribe Cenestin even though he or she wanted to?
A I don't think anybody has actually said that to me.
Q If you can turn to paragraph 26 talking about the variability.
Are you aware of any empirical data that would support there is a greater variability in what is in a Premarin tablet than what is in a Cenestin tablet?
Is there any data on that?
MS. BARTELLI: Objection. Vague.
A It's based on a reading of the U.S. Pharmacopeia.
Q The U.S. Pharmacopeia actually says Premarin has more variability than Cenestin?
A No, it says from batch to batch, and

the Cenestin information says it does not vary from batch to batch.

Q So it's your belief that Cenestin is not variable from batch to batch?

A It's my belief that the components of the Cenestin tablet are very precisely controlled to maintain the concentrations and ratios that are described, and I'm also under the impression that the FDA regularly checks that to be sure that they are doing what they say they are doing.

Q What is your basis for that? Do you think the FDA actually sits there and takes apart a Cenestin pill and determines what the components are?

MS. BARTELLI: Objection. Compound.

A My impression is that all drug manufacturers are periodically asked to have samples of their product tested. That's my impression. Maybe that's naive.

Q Are you aware of any testing that Cenestin has done that tests the degree of variability in its product?

A I believe in the, I'm not sure but I started to quote Dr. Hess's paper that we referred to earlier.

In that he describes, and I might not be not remembering this properly, that the reproducibility reproducibility, as in a birth control pill, is the same factor in making a birth control, and all of those are made very precisely with exactly what is supposed to be contained within each tablet.

My impression is that state of the art technology is being applied to the preparation of this tablet so that it delivers what it's a advertised to and doesn't vary.

I haven't seen published data about variability. My impression is that the variability is a non-issue, whether the birth pills are coming out of the their factory or Cenestin pills are coming out of their factory.

Q Let me ask you, in the first sentence in paragraph 26, you opine that the reason that the contents of individual Premarin tablets vary, and once again you are not aware of any empirical data that shows the extent to which individual Premarin tablets vary, are you?

MS. BARTELLI: Objection.

A I'm aware of the statement in the U.S. Pharmacopeia.

Q Anything else?

A Which states --

MS. BARTELLI: Objection.

A Which states that there's variability from batch to batch of Premarin.

Q Variability within some range?

A Yes, they state that.

Q Are you aware from the FDA Act requirements as to how much there can be variability in conjugating estrogen products including both Premarin and Cenestin?

A One of the issues around the U.S. Pharmacopeia in the description of Premarin is that, as you have made clear, there are ten clear estrogens which are monitored, and then as Wyeth makes clear in their package insert there are concomitant substances.

As the U.S. Pharmacopeia makes clear, one of those concomitant substances is beta Estradiol 17 beta. The natural estrogen that women make.

In editions of the U.S. Pharmacopeia that I have read, the amount of Estrodiol 17 beta has varied from 4 percent I believe to as high as 9 percent of what is in the tablet. It's a

tremendous, to my way of thinking a tremendous variability.

Again, as you pointed out from this paper, it's the most important of all the estrogens. It's not the same. It varies from 4 percent to 9 percent. Very big variability of the single most important estrogen.

Q In your opinion the Cenestin would have the same percent?

A It has no Estradiol because Estradiol is not considered one of the components.

Q But the ones it does it has the very same percentage?

MS. BARTELLI: Objection.

A I don't know the testing data and I can't quote that. I imagine they make a replicable pill and they don't include Estradiol.

Q Now you said here the reason that there's variability in individual tablets is because of the variation from one pregnant mare's urine to another.

What is the basis of your opinion in that regard?

A Tremendous variation from pregnancy to pregnancy. In one pregnancy the estrogens could be

Page 146

1,000. Another one it could be 3,000.
Q What does that have to do with what ends up in a particular Premarin pill?
You don't think that mares' urine should be boiled down and they put it into a pill. It goes through a very refined process, does it not?
MS. BARTELLI: Objection. Vague. Argumentative.
A I don't know the process it goes through. I believe that is a secret process.
Q You have no knowledge of the manufacturing process of Premarin?
A I don't.
Q Do you really have any knowledge in which you could opine that the reason for any variability in a Premarin tablet comes from the variation in the urine of a pregnant mare?
MS. BARTELLI: Objection.
A No, I don't think it's my role to explain why there's variability. I think Wyeth should explain why there is a variability.
Q Why did you do that in paragraph 47 in your report, did you think it was important to your opinion in this case?
MS. BARTELLI: Objection.

Page 147

A I think the variability is a very important issue.
Q But you also sought to express why there was a variation from one pregnant mare's urine to another, and what is the basis for that?
MS. BARTELLI: Objection.
A I know that estrogen levels vary from one pregnancy to another.
Q At the end of that paragraph you say that uneven estrogen levels can result ultimately in the frustrated abandonment of treatment rather than the search for a more effective therapy.
It's also possible, isn't it, that you could say these uneven estrogen levels can result in persistence of symptoms and ultimately the search for a more effective therapy, rather than the frustrated abandonment of treatment, as well?
MS. BARTELLI: Objection to form. Argumentative.
Q Wouldn't that be just as true a statement?
A These uneven estrogen levels can result in persistence of symptoms and the search for more effective therapy. That's a very good statement. I like that statement.

Page 148

I think we should always be looking for more effective therapy and that's what I have been trying to prescribe for my patients. So that's an excellent statement.
If we take the other part of the statement, the frustrated abandonment of the treatment, the fact of the matter is that the discontinuance rate, which again I have written about it extensively as have many, it has been an important issue obviously for Wyeth, the fact that women start and stop their drug within just a few weeks. Discontinuance rates in the first weeks are unacceptably high because of the adverse effects.
It's not working the way it should so I believe that issue is, I do believe that one of the major factors, to get back to the first part of the statement, that one of the major factors leading to persistence of symptoms and development of adverse effects are the fluctuating levels of the hormone. That's what I believe.
Q You believe that, there's no empirical data that supports that link but that is your belief, right?
MS. BARTELLI: Objection.
A I believe that in my lectures and

Page 149

writing I have published the evidence for fluctuating levels being a factor in the development of heart attacks and the development of strokes and in irregular bleeding, and I believe there's an established literature.
The issue was first provided interestingly by Dr. Speroff in 1975 and it's clear he was right. When you give a hormone replacement you should be trying to maintain a stable level, and preferably a low stable level.
Q Premarin has fluctuation in that regard as in many non-conjugated estrogens; is that right?
MS. BARTELLI: Objection. Foundation.
A The evidence that we have for Premarin is that it's a burst that releases hormones, that it has peak levels, and all of this within a very short period of time. It has peaks and troughs and for the woman taking it that is the problem.
Q Doesn't any pill have peaks and troughs?
Cenestin has peaks and troughs, doesn't it?
MS. BARTELLI: Objection. Foundation.
A Very minor peaks and troughs in

what the big findings are with Cenestin.
It could very well be exactly what you say, it's no different than Premarin. I think it contains the essential components of Premarin and I don't think, and especially from the FDA submitted data that we have it's not going to be worse.
I think it has a very good chance of being better but give it a chance. It has not had a chance.
Q 0.3-milligram of Cenestin has not been treated by the FDA for symptoms, has it?
MS. BARTELLI: Objection.
A I don't know.
MR. EGGERT: Let's take a break for lunch.
THE VIDEOGRAPER: The time is 1:21 p.m. on June 3, 2004 of the videotape deposition.
(Luncheon recess taken at 1:21 p.m.)

AFTERNOON SESSION

(Time noted: 2:27 p.m.)
PHILIP SARREL, resumed and testified as follows:
EXAMINATION BY (Cont'd.)
THE VIDEOGRAPER: The time is 2:27 p.m. on June 3rd, 2004. This is tape number three in the videotape deposition of Mr. Philip Sarrel.
(Sarrel Exhibit 5, article by Hess, Dowling and Schwartz, marked for identification, as of this date.)
Q Welcome back, Dr. Sarrel.
I place before you a document which is marked as Exhibit number 5, and it's an article by Henry Hess, Thomas Dowling and Michael Schwartz entitled "Clinical Implications of the Differences in Dissolution and Absorption Characteristics of Oral Estrogen Therapy Agents."
A This is the article that we saw before in a folder that has been marked as 11 that was published in the Journal of New Developments or something like that, yes.
Q You reviewed this document in connection with your report, right?
A Yes, I did.

Q If I could direct your attention to paragraph 34 of your report that is on page 11, you cite this report at the end of that paragraph with the proposition that Cenestin offers a distinct advantage over Premarin in the area of dissolution and absorption, right?
A That's the statement, yes.
Q Is there any other support other than this article that you are aware of for your contention that Cenestin offers a distinct advantage over Premarin in the area of dissolution and absorption?
A Under the impression?
Q Under the impression that there was what, sir.
A Under the impression that there was data that had been submitted to the FDA that was in their package insert that I had seen.
So in terms of publication in a medical journal this is the only one that I'm aware of but I do believe that another source of this information is in the package insert for Cenestin.
Q The package insert for Cenestin, can I have a copy of that? Strike that.
We will take a look at that in a

minute.
In this article here, Dr. Hess at the time this was published was the head of the medical advisory board of Barr Laboratories; is that right?
A I don't think so. Not Dr. Hess.
Q I'm sorry, is Dr. Hess, is he on the advisory board?
A He's a member of the advisory board.
Q You are the director of the medical advisory board?
A I'm the chairman of it.
Q So was Dr. Hess a member of the advisory board at the time that this was published?
A This was the document that I think indicated, at least somewhere, it was in the first quarter of the year.
But I was told before Dr. Hess told me it had not yet been published. I met him in the first meeting of the board.
This had been published in 2003, and the first meeting of our advisory board I believe was in October or November of 2003. So I don't know if I can be precise as to whether he was already a member of that or he had been asked to be a member of that.

Q You had a conversation?
A But they are very close in time and it's at that advisory board meeting where he told me that it was I thought he said in press. It may have been already been published.
Q If you are a member of an advisory board for a company and you publish an article in a journal concerning that product, would you normally disclose that fact in the article or not?
MS. BARTELLI: Objection.
A I don't know. I was looking for information from the Wyeth paper that was published in Maturitas and it's not a specific disclosure, so with respect to your question --
Q I wasn't asking about Maturitas, but if you want to talk about Maturitas the authors are identified as being with Wyeth Women's Health Research right in the caption of the article?
A Yes, but your question was whether there would be a place for disclosure, and it appears in neither of the journals is there a specific place for a disclosure.
I know there are journals where that is stated, so my impression is whether a disclosure of being on an advisory board is standard I don't

know. I imagine there is variability from journal to journal and I don't know the standard for scientific journals.
Q You don't have a personal standards that you would employ as to whether you would disclose you are a member of the advisory board and publishing an article in a journal about that product?
MS. BARTELLI: Objection to form and foundation and vague.
A No, I don't believe I would be in a situation where I would be publishing a paper specific about a particular drug submitted to a journal.
And the only journals to have been referred journals, I know the answer to the question. When you submit a paper, like for example a submission to JAMA or the New England Journal of Medicine, there is a form that you complete because I know I have completed such forms, which asks about conflict of interests and whether or not you do any kind of consulting work or lecture work or any pharmaceutical for any company that could be referred to in the course of that.
So, in fact, I have been in that

situation and I have completed such a form for the journals who do have that. What is done with that information is under the control of the editors of the journal.
Q You don't know one way or the other as to whether this journal had that practice?
A No.
Q You would agree, would you not, that this article concludes that the clinical implications of the differential of dissolution between Cenestin and Premarin have yet to be established?
MS. BARTELLI: Objection. The form and foundation.
Q I would refer you to page 94.
A Yes, they conclude "Current strategies involved selection of a modified use preparation with a uniform absorption profile to improve the consistency and predictability of estrogen because blood consistency deviates over 24 hours thereby reducing unwanted side effects and maximizing the potential for therapeutic success."
So that is their conclusion, and I think that is consistent with what I referred to.
Q Actually what they concluded on page

92 was that "Controlled pharmakinetic trials designed to compare the effect of pH altering medication on the absorption of estrogen from various ERT formulations are needed."
MS. BARTELLI: Objection.
Q There have not been such trials to date, have there?
MS. BARTELLI: Objection.
A That's a different issue. You are talking about two different issues. One is the efficacy for control of symptoms and overwhelming adverse effects, and that is one issue, and that is the issue I addressed.
The second issue about the need for studies and the influence of an antacid or a syndrome, a malabsorption syndrome, as I was referring earlier to, let's say to taking of the thyroid pill or the taking of a Lipitor pill we are aware that stomach acidity has an effect on their biovariability.
That's why the directions for the thyroid pill are not to eat for an hour after you have taken it so that you don't affect the production of acid and you don't interfere with the dissolution and absorptions.

By the way, the thyroid hormone is not very different from the estrogen hormones. It's steroid hormones.

So you have two questions on the table. One is the one I addressed, which is control of symptoms and avoiding adverse effects, and the second question the authors call for further studies.

I have to agree with them. As knowledgeable as I am, my knowledge is based on clinical observations of how the syndrome they are talking about interferes with the biovariability of the tablet which I have seen clinically.

I have situations with Premarin where the yellow tablet, the 1.25 has been passed intact into the toilet and the patient has brought it to me to say I took this pill and nothing happened and I can attest to that. That's an exaggerated situation where nothing gets into the system and is not a good situation for anything.

Q Let me ask you, though, there's no evidence that you are aware of, is there, empirical evidence that a dissolution differential between Cenestin and Premarin have an actual clinical effect?

MS. BARTELLI: Objection.

A The doctor that is the co-author states there's a need for such studies.

Q What is your view of the relationship between the shellac coating on Premarin and stomach acid? Is it the notion that the stomach acid will somehow dissolve the shellac coating?

MS. BARTELLI: Objection. Foundation. Compound.

A My understanding is that tablets with shellac coating involvement there have been many over the years that have essentially been abandoned because of their unreliability with respect to dissolution and proper absorption.

The classic example that we have had in our field of obstetrics and gynecology was a tablet called Vadectin which was given for acid of pregnancy and nausea of pregnancy and it was indeed shellac coated. From a safety point of view it was determined in the 1970s that women especially during pregnancy are exposed to the shellac and in addition it was interfering with the ability to be absorbed, and that tablet was taken off the market.

There are other examples of shellac coated pills on the market, but the progress that

has been made in science and the development of coating, most of the pills that you see or the few that you see that are left over from an earlier era with shellac coating, they are in a situation where they would have to have a drug application with a film coating in order to develop a better product.

Shellac coating is indeed a delivery system of the past, not of the immediate present or of the immediate past present. It's a mechanism of the very distant past.

MR. EGGERT: I move to strike the entire response as not responsive to my question.

MS. BARTELLI: Objection.

Q Turning to page 10 of the report, you refer to the Dowling article, and you take the position there that the article stands for the proposition that stomach acidity also plays a role in facilitating the digestion of a shellac coated product as stomach acid is necessary to dissolve coating.

Is that your understanding of what the Dowling and Schwartz article stands for?

A These authors do focus on the role of stomach pH and drug dissolution and absorption and

they do point out that there is a difference in the biovariability of different products depending on the coating around the contained drug.

Q Did they conclude that acid was necessary to dissolve the shellac coating?

A I have to look at their paper to see.

If you turn to page 94, the second paragraph, they suggest that what would happen with the reduction of the acidity would be that there would be a more rapid dissolution and a rapid absorption and then a rapid excretion, and that leads to their later conclusion that would lead to unwanted side effects, and that's something we talked about earlier.

The problem is if you have a rapid absorption and a rapid clearance, then you get a surge effect, and that's what they do refer to in this as the burst effect of the hormone.

It's the problem we were talking about earlier that I encountered with the use of micronized 17 beta Estradiol which is sold under the name of Estrace, and I told you we give it as a BID drug for this very reason, the rapid effects of rapid clearance and absorption, so you get a peak and trough very quickly which leads to symptoms like

speakers, and four of these are presented in the evening times so that doctors can call in, the doctors or nurses can call in and listen to the presentation and then ask questions.

So this is the teaching material that I was not involved in developing but I am involved in presenting, and it's meant to try to explain the impact of the Women's Health Initiative.

I think as you look through this you will see that a significant part of this is devoted to explaining the Women's Health Initiative study and its findings, and also presented a study you referred to earlier findings from the Hope study. The bone protective effects.

It's an attempt to present in a verbal way, it talks about complementary and alternative medicine and about all the different prescriptions that are out there.

The home study findings, by the way, are on pages 42 and 43, I believe, or 43 and 45. So it's education about menopause and as part of this presentation, the Cenestin preparation is described along with all the other things that are described.

Q I would like to point out this document has answers to only odd numbers in it and

perhaps the even numbers were not copied?

A That looks that way to me.

Q I request a copy of the document with the even numbered pages.

A What I submitted was the whole document.

Q Probably it is an error in duplicating.

Have you presented this yet?

A There is maybe another pile on the table with the even pages.

Q Have you presented this already?

A I presented it twice. There are two evenings in May that I was the speaker, and I will be presenting it again on June 30 and July 1st.

Q You said that's by Barr or by Duramed?

A I'm being paid by Access, which is the educational company. I haven't been in contact with Barr about this at all.

I was invited by Access which is the educational company hired by Barr. They have independently developed these teaching materials and I would not actually have put the program together the way you see it but because I'm one of their resource people I was invited to be a presenter, and

so of the hundred or so nights four of the nights will be mine.

Q Those are the actual slides you will be using in the presentation?

A The presentation will be to go from slide to slide and explain to the doctors that are listening.

(Sarrel Exhibit 15, educational program, marked for identification, as of this date.)

Q If I could show you a document entitled "The New Generation of Conjugated Estrogens. The Conjugated Estrogens Combining Past Tradition with Advances in Technology."

Would you explain what this document is?

A This is another educational program which was prepared for the Interactive Network for Continuing Education.

It's related to the first document that you showed me, which was the CD Rom.

Q Referring to Exhibit 13?

A Right. That program and this program are the same.

This program was presented where once

again there was a presenter, Dr. Hess, and I was the moderator, and in this program if you want you can look into it, my credentials and disclosures as you can see are there at the beginning of the program.

Then what we have, and I could tell you quite precisely that I presented the first slides, I just presented the first three slides at which point Dr. Hess took over and presented the rest.

At the end of approximately 25 minutes we were finished with taking the listeners through this, and then they called in individually and that was taped, and then from the tape we prepared what you see in the workbook here.

The first thing you showed me, the little workbook in the back you have the Q and A questions. The whole front of the workbook is the same as this and the back of it is the Q and A's.

MR. EGGERT: This is Exhibit number 16.

(Sarrel Exhibit 16, record of Q and A, marked for identification, as of this date.)

Q That's the document you were just referring to?

A That's right.

Page 262

Q That's also entitled "The New Conjugation of Estrogens," and this is a record of the questions and answers that were done in connection with the slides?
A Doctors who were not able to call in on the nights we gave this. We only gave this 12 times. This was not given 100 times. This was given 12 times, and then doctors who were not able to call into that had another option, that is, they could obtain, they could go to the Interactive Network of Continuing Education and obtain the package that you have of the smaller program, listen to the CD and do the test and send it in and receive continuing medical education credit.
So that way I was able or Dr. Hess and I were able to reach out to a larger group of doctors.
Q Once again, the answers you provided to the questions in this document were true and accurate?
A Yes.
Q Are there any other presentations that you have participated in or helped develop for Cenestin?
A No, I tried to bring you what I had,

Page 263

including really up to the present, you have what is happening now in June of 2004.
Q Since the time of your last deposition in the Duramed case, have you done anything to educate yourself to learn more about the nature of management care of formulary?
MS. BARTELLI: Objection. Foundation.
A No.
Q Have you reviewed any of the literature that might be available on the subject of management care of formularies?
A No.
Q Are you familiar with the concept of a PBM or a pharmacy benefit management?
A I have heard the letters and I could not give a job description of such a person.
Q Do you think it's a person, an individual who would be hired to be a pharmacy benefit?
MS. BARTELLI: Objection.
A I really don't know.
Q Are you familiar with a entity known as advanced PDS?
A No.
Q Do you know what kind of formulary PCS

Page 264

has? I gather not.
A I do not.
Q Do you know what the distinction is between an open formulary and a closed formulary?
A Those are terms that I haven't heard. I'm told that what we have at Yale is an open formulary, and that's the system I have worked in for all these years which has translated into whatever the health-care providers had felt they wanted to prescribe or was the best treatment for their patients that we could do that. That is an open formulary.
So we have not a received a list that says this is our formula and this is the only thing you can order through the health plan.
From listening to doctors and meeting with doctors across the country they are in quite different situations where they get a list or a booklets that lists the drugs on their formulary and that are recommended that they prescribe, and some places I have been told that they can't prescribe anything other than those drugs.
I don't know if that is the definition of a closed formulary. I'm told if doctors have a drug, even when it's not listed, there is a

Page 265

mechanism through which they can apply and hopefully be able to prescribe it, and have it covered for their patients, but it's a very difficult and tedious thing to do.
Q Do you know the particular management care plans that those doctors were affiliated with that you spoke to about that?
A I can't remember the names. At one point I could.
Q Do you remember the states in which they were located?
A Yes, the one I remember most distinctly because it took us two full years for them to get a proper drug. I suppose they were dealing with a closed formulary because the management care group that controlled the Hudson Valley, that is not far from here in New York state, did not have the drug that I was indicating in my lecture was the safest drug to give women, a progesterone preparation, but it took them over two years and it took a signing of an appeal by the entire staff of the Vassar Brothers Hospital in Poughkeepsie, New York to accomplish getting this one drug on the formulary.
Q They were successful in doing so?

A After two whole years. In the interim the alternate drug, the drug that we wanted, that was natural progesterone.

My research had shown that natural progesterone was the safest progesterone that women could take to balance their effects of estrogen in the uterus.

By this time we had known that Provera, the alternate drug that was so widely used, would induce strokes and they, unfortunately, experienced a number of strokes within that community which is what so strongly motivated doctors to win this battle against the formulary.

Q Are you aware of any circumstances in which physicians have felt strongly and banded together to try and insure that Cenestin can be on the formulary?

A I'm not aware of that.

Q Have you ever suggested that to any physicians that they should attempt to do that?

MS. BARTELLI: Objection.

Q As you did with Prometrium?

A I really haven't been in a position to do that. All of my lecturing across the country has been academic and I am an invited professor and

grand rounds, and focused on the issue in the last two years, focused on understanding the findings of the Women's Health Initiative and why this does not apply to other hormone treatments.

I haven't been a speaker for Cenestin except in this series during the four evenings, and that question might have been raised by a doctor that is not on the formulary but it has not been raised. I haven't been asked that.

Q Do you have any knowledge as to the extent to which Cenestin is currently listed on the indicated formulary list?

A I only know in my own practice there has been no difficulty to get it for patients and the gynecologists who work in the Yale health plan and the midwives have been able to prescribe that. But that is what I would guess an open formulary.

Q Do you have any sense as to what percentage of formularies are closed formularies in the country?

A No, it's not something that I would be knowledgable about at all.

Q Are you familiar with the concept of a tiered formulary?

A Vaguely.

Q What do you understand a tiered formulary to be?

A I am probably wrong. I believe it means that there is the recommended first line of drugs and then there are alternate drugs that can be prescribed, if requested, so that there is actually a listing of, and I think that is what tiers refers to?

Whether there are two or three tiers I don't know, but that's very different from a drug not being listed at all.

Q In paragraph 51 of your report, the second sentence on page 16 you state that "When nonformulary alternatives are allowed there usually is a process requiring a formal request and approval by the pharmacy review board of the managed care organization."

Is it your actual understanding that with respect to any managed care plan that the pharmacy review board of the managed care entity has to approve each request by a physician to prescribe a drug which is not on the formulary?

A I know that was the experience in Poughkeepsie.

Q It was with respect to Prometrium?

A Yes, I believe it was the process in Madison, Wisconsin and the other site that I referred to.

I had been invited to lecture at the University of Wisconsin over a period of five or six years and over all of that time I had indicated to them how one formal treatment would be detrimental and another be safer, and so they started and it took them years to get it changed.

I believe they had it changed for the whole State of Wisconsin. I could be wrong. I believe that has finally opened up.

Q Any other formulary other than in Poughkeepsie and Madison, Wisconsin, of which you are familiar in this regard?

MS. BARTELLI: Objection. Vague.

A Not in this one. For many physicians already time stressed by the demand of current medical practice the frequent result is that the path of least resistance is a prescription of the drug on the formulary rather than a prescription of a nonformulary drug.

The path of least resistance, that is which is easier to do given the limited amount of time that a physician has, what doctors have